REMARKS

Method claims 39-56 and 65-75 remain pending in the application. Claims 57-64 and claim 76 have been cancelled in order advance prosecution of the present application. Claims 39-76 were rejected in the July 12, 2011 Office Action. Independent claims 39, 48 and 65 having been amended. Support for the amendment to the claims can be found throughout the originally filed specification, examples and claims and in particular, in Table 1 on page 23 and Figure 8 (see compound E11-2,2Rev) which indicates that that compound does not exhibit SERM activity and is therefore excluded from each of the pending independent claims. No new matter has been added by way of the present amendment.

Applicant respectfully requests that the method claim amendments presented herein be entered in the application as they respectfully submit that they place the application in a condition for allowance. Applicant maintains for the reasons explained below that method claims 39-56 and 65-75 as amended herein are allowable and should be passed to issue. Applicant addresses each of the Examiner's concerns in the sections which are presented hereinbelow.

The undersigned attorney respectfully acknowledges the courtesy of the brief telephonic interview Examiner Badio conducted on short notice on December 1, 2011 to narrow the issues to be addressed in this office action. The interview summary record which was prepared by Examiner Badio accurately reflects the discussions which were had during that interview.

The Examiner has variously rejected the previously pending claims under 35 U.S.C. §§112 and 103 for the reasons which are presented in the July, 2011 office action on pages 2 through 11. Applicant shall address each of the rejections in the sections which follow.

The Rejection of Previously Pending Claims 57-64 Under 35 U.S.C. §112, First Paragraph

In the July, 2011 office action, the Examiner rejected previously pending claims 57-64 as failing to comply with the written description requirement. Applicant has reviewed claims 57-64 and the Examiner's rejection and acknowledges that the Examiner appears to be requesting experimental data to support the patentability of claims 57-64. Although Applicant respectfully disagrees with the Examiner's characterization of the rejection and respectfully submits that the phrase "reducing the likelihood of a recurrence of estrogen-sensitive breast cancer in a patient" satisfies the written description requirement, further discussion of this rejection has been mooted by the cancellation of claims 57-64, those claims to which the Examiner's rejection has been directed. Applicant notes that the reason for his cancelling of claims 57-64 at this time is to attempt to marshall further evidence in support of the patentability of claims 57-64 and to present that evidence, in a divisional and/or continuation application, if appropriate.

The Rejection of Previously Pending Claim 76 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected previously pending claim 76 under 35 U.S.C. §112, Second Paragraph for the reasons which are presented in the July, 2011 office action on pages 4-5. Given that Applicatio has canceled claim 76, no further discussion of this rejection is deemed necessary.

The Rejection of Previously Pending Claims 39-75 Under 35 U.S.C. §103 As Being Obvious Over van den Broek

In the July 12, 2011 Office Action, the Examiner had rejected of claims 39-75 under 35 U.S.C. § 103(a) as being unpatentable for obviousness over U.S. Patent No. 3,972,906 ("*van den Broek*"). According to the Examiner, at the time of the invention of

the pending claims, the use of *van den Broek's* estrogenic compounds to be used in the present claimed invention to treat menopausal symptoms and breast cancer as claimed would have been obvious. Applicant notes that previously pending claims 57-64 and claim 76 has been cancelled from the present application.

Essentially, the Examiner argues that the disclosure of van den Broek renders the present invention obvious despite the fact that van den Broek provides no working examples of compounds which are used in the present invention; relies for a determination of obviousness based upon the teaching of alternative and nonpreferred examples, not lead compounds; and the fact that despite the fact that the presently claimed methods exemplify the unexpected activity exhibited by the claimed compounds and unrecognized by van den Broek, because the "Discovery of a new activity of a prior art compound does not lend patentability to the utilization of said compound(s) in the method as taught or made obvious by the prior art." The Examiner further contends that the presently claimed compounds do not evidence unexpected activity consistent with the scope of the claimed compounds. Finally, the Examiner contends that van den Broek teach a genus of compounds useful in treating estrogen-deficiency syndromes, that menopausal symptoms and breast cancer are estrogen-deficiency syndromes and thus the use of van den Broek compounds in treating menopause symptoms and breast cancer would have been obvious at the time of the present invention. For these reasons, the Examiner maintains her rejection of the previously pending claims as being obvious over the teachings of van den Broek. Applicant respectfully traverses the Examiner's rejection.

Applicant agrees with the Examiner in her characterization of the issue of obviousness/non-obviousness to be resolved, but notes that Van den Broek's teachings are such that they would not have given rise to the currently claimed methods and are, in fact, incompatible with the *method* claims of the present invention. This is based upon Applicant's discovery that the compounds which are set forth in the present *method* claims exhibit unexpected selective estrogen receptor modulating (SERM) activity which

are used in methods which make use of that unexpected activity *to the exclusion of the activity which is taught by* ***van den Broek.*** It is Applicant's view that the presently claimed methods are directed to uses of compounds which rely on the activity which could not be surmised or determined from the teachings of van den Broeck. It is Applicant's view that the currently claimed methods are non-obvious over the teachings of van den Broeck. Applicant notes that the present methods *only* become available as methods ***because*** of the discovery of the unexpected SERM activity of the compounds, without which the compounds would not have even been used in the methods of van den Broek.

Thus, Applicant respectfully contends that the compounds set forth in the present *method* claims evidence unexpected activity as selective estrogen receptor modulators (SERMs) and this unexpected activity, which was completely unrecognized by and non-obvious over the teachings of van den Broek, results in claimed methods which are clearly non-obvious, patentable and distinguishable over the teachings of van den Broek, which issued in 1976[1].

Applicant's claimed methods represent the first use of steroidal SERM's:
(a) to treat the menopausal symptoms as claimed in a patient while reducing the risk that the patient develops, or experiences a recurrence of, an estrogen-sensitive cancer;
(b) to treat an estrogen-sensitive cancer; and
(c) to treat the symptomology of menopause as claimed in a patient suffering from an estrogen-sensitive cancer.

In each of the claimed methods, which represent generic methods as set forth in independent claims 39, 48 and 65, the method relies on the unexpected and previously unknown activity of the present compounds which exhibit a combination of

[1] Applicant points out the issue date of van den Broek only to emphasize the point that if van den Broek had taught or suggested the present invention as the Examiner argues, surely one of ordinary skill would have discovered the highly desirable SERM activity of the putatively disclosed compounds of van den Broek well before Applicant's invention in 2002, some *twenty-six* years later.

estrogenic/anti-estrogenic activity, to produce a favorable therapeutic result precisely ***because of the unexpected and previously unknown estrogenic/anti-estrogenic activity of the compounds used in the presently claimed methods.***

All of the presently claimed methods rely on the unexpected SERM activity (i.e., the unexpected combination of estrogenic/anti-estrogenic activity) to produce a favorable therapeutic result for the claimed methods and clearly distinguish over the teachings of van den Broek, which completely failed to recognize this unexpected SERM activity. Contrary to the Examiner's contention, the skilled practitioner, based upon the teachings of van den Broeck would not have recognized the activity of the present compounds as SERMS, and would, therefore, not have even thought to use these compounds (even if taught by van den Broeck) in the methods of the present invention.

At the time of the invention of the pending claims, the non-steroidal SERM Tamoxifen® was indicated for the treatment and prevention of breast cancer. It was recognized that post-menopausal patients treated with Tamoxifen® could benefit from a potential reduction in bone loss and cholesterol levels. Also, at the time of the invention of the present application, the use of steroidal estrogen receptor ***agonists*** such as those disclosed by the art of record (van den Broek) to treat post-menopausal symptoms were associated with an enhanced risk of breast cancer in that therapy and ***contraindicated*** specifically for those reasons. The present invention addresses the concerns of the art with the unexpected discovery that *steroidal* compounds which are presently set forth in the method claims of the present invention exhibit unexpected SERM activity and reflect a pharmacological activity profile consistent with SERM compounds of the prior art, but completely unknown for steroidal compounds. It is that discovery, combined with the use of that unexpected pharmacological profile in methods which exhibit therapeutic efficacy because of that and consistent with the pharmacological profile of a SERM that is the essence of the present invention. This is nowhere to be found in or to be gleaned from the disclosure of van den Broek.

Applicant respectfully submits that van den Broek does not teach or suggest that *any* of the compounds which are disclosed therein exhibit selective estrogen receptor modulator (SERM) activity as in the present invention. Rather, van den Broek teaches a myriad number of compounds which exhibit a broad range of activities which include contraceptive, estrogenic, progestational, ovulation-inhibiting, gonad-inhibiting and anabolic properties. There are many thousands of compounds disclosed in van den Broek and many different general biological activities associated with the large number of disclosed compounds, even though no hard biological activity from which one could identify an actual lead compound is ever provided in van den Broek. Van den Broek is primarily directed to chemical compounds and the disclosure set forth in that reference is almost exclusively devoted to chemical compounds and chemical synthesis of those compounds.

There is absolutely ***no*** biological activity of *any* of the compounds which are set forth in the present claims. None of the biological activity of the presently claimed compounds is exemplified and presented in van den Broek. ***None.*** There is no biological activity of any of the compounds of van den Broek specifically exemplified and there is no structure activity relationships developed from which one of ordinary skill in the art could glean an activity profile from the disclosed compounds in van den Broek. Thus, with respect to the biological activity of the present compounds putatively disclosed in van den Broeck, that activity must be described as, at best, *propheticor mere guesswork*, and more accurately, completely non-disclosed. That is, if one of ordinary skill wanted to identify the biological activity of a number of the compounds which are set forth in the presently claimed invention which are putatively disclosed in van den Broek[2], that person of ordinary skill would have had to make the compounds and test the compounds' activity. There is no disclosure in van den Broek as to what that biological activity would be and if one of ordinary skill *actually* made the *putatively* disclosed compounds used in

[2] Applicant maintains that van den Broek does not disclose the presently claimed compounds and to the extent that one of ordinary skill might surmise that the presently claimed compounds might exhibit estrogen agonist activity, that person of ordinary skill would be disabused from such a teaching after those putative compounds were actually made and tested and exhibited anti-estrogenic activity in the relevant assays.

the present invention, that person would find that the compounds used in the present methods did *not* possess the activity desired (estrogen agonist activity) by van den Broek in the relevant estrogenic assays. Thus, even if one of ordinary skill in the art attempted to duplicate the putatively prophetically disclosed compounds used in the present invention to map out a structure activity relationship, that person of ordinary skill would have found that the compounds used in the present invention did not possess the activity desired by van den Broek, because the present compounds are actually ***antagonists*** (i.e., not agonists) in the relevant estrogenic assays used by van den Broek. Whereas van den Broek required agonist estrogenic activity, the presently claimed compounds exhibit ***antagonist*** activity and would be viewed by van den Broek as undesirable and not useful for the purposes taught by van den Broek (in applications where agonist estrogenic activity was used). Thus, from the standpoint of the common sense workings of the person of ordinary skill relying on the teachings of van den Broek, the compounds of the present invention exhibit ***undesirable*** activity. It is not until the present invention that one of ordinary skill would have recognized that the undesirable activity of the present invention could actually be used favorably in a therapeutic method. It is respectfully submitted, that the present invention represents the essence of invention.

With respect to the suggested estrogenic activities of the van den Broek compounds, the only estrogenic activity disclosed or suggested therein appears in column 2, lines 28-48, where van den Broek discloses that certain ***short-chained*** 11β-substituted steroidal compounds (in contradistinction to the present invention) exhibit estrogenic (agonist) activity. In particular, van den Broek cites a number of specific compounds with different pharmacophores as exhibiting estrogenic activity. However, the ***only*** specifically disclosed compounds relevant to the present invention and having a similar estradiol pharmacophore to those used in the present invention are 11β-methoxymethyl-ethinyl-estradiol and 11β-chloromethyl-ethinyl-estradiol, both having short-chained groups at the 11β position of the compound, not the longer chained groups at the 11β position (at least 5 non-hydrogen atoms in the chain) as is required by the present invention.

In particular, the estradiol compounds of van den Broek have a methoxymethyl group or a chloromethyl group at the 11β position of estradiol and an ethinyl group at the 17 position of estradiol. See, van den Broek, column 2, lines 28-48. It is noted that every compound which is *specifically* disclosed by van den Broek as having estrogenic (agonist) activity has a *short-chain group* at the 11β position of the steroidal pharmacophore, i.e., a chain-length of 3 (methoxymethyl) or 2 (chloromethyl) non-hydrogen atoms, regardless of pharmacophore. None of the other compounds is specifically disclosed in van den Broek as having estrogenic activity. This is consistent with the examples provided by the present application where, as claimed, unexpected SERM activity resides in similar steroidal compounds where the 11β-chain contains at least 5 non-hydrogen atoms in the chain.

The biological activity (estrogen agonist activity) suggested in van den Broek for the disclosed short-chain 11β substituents (methoxymethyl or chloromethyl) is corroborated by the experiments presented on pages 22-25 of the present application. Indeed, a review of the structure activity relationship related to 11β substituents of estradiol in the present application (see especially tables 1 and 2 on pages 23 and 24) evidences that the short-chain compounds which are *specifically* disclosed by van den Broek do *indeed* exhibit estrogenic activity, but when the 11β side-chain is lengthened to 5 or more non-hydrogen atoms as presently claimed, the compounds become ***anti***-estrogenic exhibiting SERM activity, an unexpected result, and a result which stands in complete contrast to the biological activity of the compounds disclosed by van den Broek. The compounds of the present invention exhibit *anti-estrogenic* activity consistent with their activity as SERMS, not estrogen agonists, as taught and required by van den Broek. Van den Broek does not disclose or suggest the pharmacological activity (SERM) of the presently claimed compounds. Given the clear deficiency of van den Broek, van den Broek clearly does not disclose or suggest the methods of the present invention which rely on the unexpected (and non-disclosed by van den Broeck) SERM activity of the claimed compounds in order to favorably practice the presently claimed

methods, which are completely distinguishable from the prior art teachings of van den Broeck. Moreover, the compounds which are set forth in the present method claims would not be used as estrogen agonists, because they do not exhibit estrogen activity consistent with the teachings and requirements of compounds of van den Broek.

It is respectfully submitted that the estrogenic compounds which are disclosed by van den Broek are *contraindicated* for use in the presently claimed methods and consequently, van den Broeck *teaches away* from the present invention. For example, each of the methods which are presented in independent claims 39, 48, 57 and 65 rely on the unexpected SERM activity of the claimed compounds in order to effectively and favorably practice the claimed invention. That is, in order to favorably practice the present invention, estrogen antagonist activity, not agonist activity, is actually beneficial for practicing the present invention. Applicant notes that estrogen agonists such as those disclosed and favorably required by van den Broek are *contraindicated* in patients with or at risk for estrogen-sensitive cancer such as breast cancer, and estrogen agonists ***worsen***, rather than *treat* these cancers, whereas the present compounds, which exhibit unexpected anti-estrogenic activity in those tissues where estrogen-sensitive cancers develop, provide meaningful utility and beneficial therapy in the methods of the present invention. This stands in complete contrast to the teachings of van den Broek, which do not and cannot provide the beneficial therapy of the present methods because the estogenic activity of those compounds would worsen, not treat the estrogen sensitive cancers. Moreover, following the teachings of van den Broek would *never* result in the present invention.

The presently pending claims make use of the unexpected activity exhibited by the claimed compounds. Thus, in claim 39, which is directed to a method for treating menopause while reducing the risk that a patient will develop an estrogen-sensitive cancer, the SERM compounds as claimed are particularly useful because they are effective against estrogen-sensitive cancer, whereas van den Broek taught estrogenic compounds are *contraindicated* because estrogen agonists actually *increase* the risk of estrogen-sensitive cancers. In claim 48, which is directed to treating an estrogen-

sensitive cancer in a patient, treatment is favorably provided by the SERM compounds of the present application because of the unexpected anti-estrogenic activity displayed in the estrogen-sensitive cancer tissue, whereas the van den Broek estrogenic compounds are *contraindicated* (see the discussion below and the previously submitted declaration of Dr. Richard Hochberg, in paragraph 12). Likewise, in claim 65, which is directed to a method for treating menopause in a patient with an estrogen-sensitive cancer, the compounds according to the present invention exhibit favorable activity in treating the symptomology of menopause without exacerbating estrogen-sensitive cancers (because they are estrogen *antagonists* in estrogen-sensitive tissues), whereas the van den Broek compounds are contraindicted for the method of claim 65 because of the disclosed estrogenic agonist activity, which exacerbates/worsens estrogen-sensitive cancer and is contraindicated in estrogen-sensitive cancer. The same is true for all of the remaining claims, which are dependent on claims 39, 48, 57 and 65.

Thus, contrary to the Examiner's contention, the compounds which are presented in the pending method claims exhibit unexpected activity when used in the pending methods and this unexpected activity and the pending methods are not taught or suggested by van den Broek. As explained, van den Broek actually *teaches away* from the present method claims inasmuch as the biological activity which is taught by van den Broeck is *contraindicated* in the claimed methods and the present compounds do not possess the estrogenic activity which is required by van den Broek in any event. There can be no greater evidence of non-obviousness over a reference than when that reference, when used within the context of its teachings, teaches something which should be avoided or can't even provide the required activity (as taught by van den Broek) in the first place.

In short, the presently claimed methods deviate from the prior art precisely at the point of invention where the present invention is favorably used because of the unexpected biological activity (SERM) exhibited by the claimed compounds, whereas the compounds of the prior art are actually contraindicated. The Examiner's argument that

the compounds disclosed by van den Broek would *inherently* produce the claimed methods is not credible, given that the compounds which are claimed in the present methods are *not* specifically disclosed by van den Broek in the first instance, and if one of ordinary skill were to *theoretically* make compounds according to the present invention and test those compounds in a traditional estrogen assay (see the previously submitted May 2, 2007 declaration of Richard Hochberg, and in particular at paragraph 19), that person of ordinary skill would have realized that the compounds had no art recognized estrogen agonist activity. Based upon the teachings of van den Broek, the person of ordinary skill would have concluded that the compounds set forth in the presently claimed *method* claims, in essence, did not have the requisite taught estrogen agonist activity and would be seen as essentially *useless* for the purposes for which estrogen agonist compounds are taught in van den Broek.

Applicants further submit that the presently claimed compounds as having SERM activity are not taught by van den Broek and one of ordinary skill would not have been motivated to make and use the present compounds in the presently claimed methods which rely on SERM activity, given the teachings of van den Broek. Applicants respectfully submit that the compounds according to the present invention, which exhibit anti-estrogenic activity in traditional estrogen receptor models (see paragraphs 14-22 of the previously submitted declaration of Dr. Richard Hochberg dated May 2, 2007, enclosed) would not have been considered useful by van den Broek for treating menopause, because menopause treatment traditionally required estrogen agonist activity in the vagina and uterus, to address vaginal dryness and hot flushes, whereas the present compounds, are anti-estrogenic in the vagina and uterus. Thus, the unexpected SERM activity which is exhibited by the present compounds stands in complete contrast to the desired activity (estrogenic agonist) of van den Broek and would not be considered appropropriate or even useful. Moreover, van den Broek does not disclose SERM activity of any of the disclosed compounds and provides no basis upon which a structure activity relationship could be inferred. Applicant respectfully submits that it is certainly

not obvious to use a compound whose activity is not known in a method which requires that activity.

Based on what was known in the prior art and their own knowledge, those of ordinary skill in the art at the time of the invention of the pending claims would have reasonably believed that the presently claimed SERM compounds would have failed to achieve the purposes of the van den Broek taught methods *and* separately, the purpose for which the currently claimed methods are applied, precisely because of the unknown and unexpected (SERM) activity exhibited by the presently claimed compounds. *See Takeda Chem. Indust. v. Alpharma Pty Ltd.*, 492 F.3d 1350; 2007 U.S. App. LEXIS 15349; 83 U.S.P.Q.2D (BNA) 1169 (Fed. Cir. 2007), *cert. denied*, 2008 U.S. LEXIS 3015 (U.S., Mar. 31, 2008).

Regarding the Examiner's arguments that a compound and its properties are not separable, Applicants merely point out that while that basic tenet is true, the actual compounds used in the present invention exhibit substantially different and unexpected pharmacological activity from the activity of compounds taught by van den Broek and the methods of the present invention make use of these activity differences between the compounds used in the present invention and the prior art taught compounds. While it is true that one cannot separate a compound from its properties, where, as here, the properties of the compounds deviate from the teachings of the prior art and Applicant makes (new) use of those newly discovered properties in a way that clearly relies on and distinguishes that unexpected activity from the teachings of the prior art, invention exists. This is well settled law.

It is Applicant's further respectful position that the Examiner's obviousness rejection ignores both the purposes for which the claimed methods are administered and the advantages of those methods, and further presupposes knowledge on the part of skilled artisans about the nature and properties of the administered compounds that could have only been gained from Applicant's invention. Van den Broek clearly did not

disclose SERM activity for any disclosed compound, let alone compounds used in the present invention. Such a hindsight reconstruction of the prior art is legally impermissible. *See Ortho-McNeil Pharma., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 86 U.S.P.Q.2d 1196 (Fed. Cir. 2008) (*KSR* posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness; only by impermissible hindsight could patentee's selection and modification of a compound putatively developed for a different application be found obvious in this instance).

Regarding the Examiner's view that the presently claimed methods do not provide a scope consistent with the asserted unexpected results, Applicant points to the fact that the claimed compounds do possess SERM activity consistent with the scope of the claims, as evidenced by the teachings of the present specification as set forth in the examples and in particular, in Tables 1 and 2 and the relevant text on pages 23 and 24.

The Non-Obvious of the Present Claimed Invention is Supported by Relevant Caselaw

The analysis of obviousness of the present invention must be viewed through the prism of the recent C.A.F.C. decision, *Unigene Laboratories, Inc. v. Apotex, Inc.* (August, 2011), copy enclosed for the Examiner's review. The *Unigene* case sets the standard for an analysis of obviousness of pharmaceutical compounds post-KSR (KSR International, Inc. v. Teleflex, Inc., KSR INT'L CO. v. TELEFLEX INC. (No. 04-1350) 119 Fed. Appx. 282 (2007). In *Unigene*, the C.A.F.C. set the standard for obviousness by establishing that requirement for identifying a "lead compound" to serve as a starting point for establishing obviousness. As the Court said in *Unigene* (at page 15, with reference to the obviousness of a claimed compound):

> To render a claim obvious, prior art cannot be "vague" and must collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution. *Bayer Schering.*, 575 F.3d at 1347. Indeed, "most inventions that are obvious were also obvious to try," *id.*, and a combination is only obvious to try if a person of ordinary skill has "a good reason to pursue the known options." *KSR*, 550 U.S. at 421. When a field is "unreduced by direction of the

> prior art," and when prior art gives "no indication of which paramcters were critical or no direction as to which of many possible choices is likely to be successful," an invention is not obvious to try. *Bayer Schering*, 575 F.3d at 1347 (citing *O'Farrell*, 853 F.2d at 903); *see also Ortho-McNeil*, 520 F.3d at 1364 (stating the number of options must be "small or easily traversed").
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> A prima facie case of obviousness in the chemical arts is often based on a known compound, called a "lead compound," which serves as a starting point for a person of ordinary skill developing the claimed invention. *See Eisai*, 533 F.3d at 1357. Where the patent at issue claims a chemical compound, a lead compound is often used to show structural similarities between the claimed compound and prior art. *Id.* (citing *Eli Lilly*, 471 F.3d at 1377).

Based upon the Court's findings in *Unigene*, Applicants respectfully submit that the presently claimed compounds are non-obvious over the teachings of van den Broek. A review of van den Broek evidences that the compounds which the Examiner references as being structurally closely related to the presently claimed compounds *are not lead compounds* and are listed amongst a large number of related compounds. Indeed, in van den Broek, there is no evidence of any lead compound because there is no biological data which can serve to provide an indication of a lead compound. The van den Broek cited compounds are not even indicated as having any relevant activity, are not presented in the examples section and the van den Broek disclosure provides no basis upon which a structure activity relationship could be inferred. Indeed, if the person of ordinary skill did conduct his or her own structure activity relationship, that person would find that the presently claimed compounds do not contain the agonist estrogen activity desire and taught by van den Broek. In complete contrast, the compounds according to the present invention which are relevant to the van den Broek disclosed compounds exhibit unexpected activity as SERM compounds. Given that van den Broek cites a huge number of compounds, does not provide the compounds cited by the Examiner as lead compounds and provides no guidance *whatsoever* as to the nature of the impact of the various substituents on the pharmacological activity of the compounds which are disclosed except perhaps to lead the person of ordinary skill *away from* the desired activity requied by the prior art, the presently claimed compounds are clearly non-obvious over the teachings of van den Broek.

Accordingly, Applicant maintains that claims 39-75 are clearly nonobvious over van den Broek.

The Rejection of Previously Pending Claims 39-75 Under 35 U.S.C. §103 As Being Obvious Over van den Broek in view of Cameron, Palkowitz and Bodor

The Examiner has rejected previously pending claims 39-76 under 35 U.S.C. §103(a) as being unpatentable over van den Broek, in view of Cameron, U.S. patent publication no. 2001/0025051 ("Cameron"), Palkowitz, U.S. patent no. 6,268,361 ("Palkowitz") and Bodor, et al., U.S. patent no. 4,617,298 ("Bodor") for the reasons which are set forth in the July, 2011 office action on pages 9-11. Essentially, the Examiner argues that because estrogen was known to be used to treat "estrogen-sensitive" cancer, as well as the symptoms of menopause, as taught by Cameron, Palkowitz and Bodor, it would have been obvious to the skilled artisan to treat estrogen-deficiency syndromes such as menopausal symptoms, osteoporosis and estrogen-dependent cancer using the compounds as taught by van den Broek. As the Examiner states "The issue is not whether the use is contraindicated, but whether said use was made obvious by the cited references". Applicant agrees that the Examiner has correctly framed the issue and respectfully traverse the Examiner's rejection for the following reasons.

The teachings of van den Broek and the failure of the prior art to recognize the existence of SERM activity in any of the compounds disclosed in van den Broek, or the benefits that SERM activity provides in relationship to the claimed methods, discussed in detail hereinabove, is referenced here. In essence, van den Broek failed to teach the unexpected pharmacological activity of the presently claimed compounds which are used in methods according to the present invention which rely on that activity, and the known pharmacological activity as taught by van den Broek is *contraindicated* for use in the presently claimed methods. It is the clearly distinguishable and unexpected SERM

activity of the compounds as presently claimed in methods which rely on and distinguish over the prior art estrogen agonist compounds based upon that unexpected activity which forms the basis and foundation of the patentability of the present invention.

Van den Broek does not disclose or suggest the present invention for the reasons which are presented hereinabove. In the first instance, the teachings of van den Broek do not provide a teaching that the compounds used in the present invention have the requisite estrogenic ***agonist*** activity which is required by the teachings of van den Broek. In fact, the opposite is true. That is because the compounds used in the present invention do not exhibit the estrogen agonist activity that is recognized and required by the teachings of van den Broek. In complete contravention to van den Broek, the compounds used in the present invention exhibit anti-estrogenic activity (i.e., estrogen antagonist activity), not the estrogenic activity recognized and promoted by the teachings of van den Broek. The pharmacological profile and activity of the compounds used in the present invention work in a manner completely inconsistent with the teachings of van den Broek and would not be used because of the van den Broek teachings and the acitivity of the presented used compounds. Van den Broek clearly does not disclose or suggest the present invention.

None of Cameron, Palkowitz or Bodor, taken alone or in any combination, cures the deficiencies of van den Broek in failing to suggest the present invention. Much of the disclosure of Cameron, Palkowitz and/or Bodor is actually irrelevant to the present invention, because the claimed compounds and pharmacophores disclosed in each of those references are simply unrelated to the present invention. There is no possibility of generating a structure activity relationship of any relevance whatsoever to the compounds of van den Broek from the disclosures of Cameron, Palkowitz or Bodor. From this perspective the present invention is not only *non-obvious* over the teachings of Cameron, Palkowitz or Bodor, but is largely *inapposite* (i.e., irrelevant) to the teachings of these references.

The more generic disclosure of Cameron, Palkowitz or Bodor upon which the Examiner relies, as to the use of estrogen agonists in the treatment of estrogen-sensitive cancers, actually *supports* the *non-obviousness* and patentability of the present invention, rather than the Examiner's position that the present invention is obvious. This is because the compounds of the present invention *are not the desired estrogen agonists* as taught by van den Broek, but rather *estrogen antagonists*, which van den Broek fails to recognize has favorable activity. Indeed, as explained hereinabove, van den Broek emphasizes estrogen agonist compounds having a short-chain at the 11β position, rather than the selective estrogen antagonist activity of long-chain compounds of the present invention which are useless in the teachings of van den Broek. Applicant further notes that the present invention actually disclaims the use of compounds similar to those disclosed by van den Broek which evidence estrogen agonist activity.

The prior art relied on by the Examiner again, *teaches away* from the present invention. Applicant notes again that the present claims are directed to *methods* which use compounds which are undisclosed by van den Broeck, i.e., compounds possessing SERM activity and utilize the unexpected activity of these compounds to produce therapeutic results which rely on that unexpected activity in complete contravention to the teachings of van den Broeck. The teachings of Cameron, Palkowitz or Bodor related to the use of estrogen agonists which are combinable with the teachings of van den Broek simply emphasize the use of the van den Broek disclosed short-chain 11β compounds exhibiting agonist activity, ***not*** the long-chain 11β compounds which exhibit an unexpected SERM activity favorably used in the methods of the present invention.

By way of example, Cameron is directed to certain compounds for preventing breast cancer. These compounds, which are completely unrelated structurally to the present invention, are said to be useful for preventing breast cancer. The teachings of Cameron have little to do with the present invention other than to point out that estrogen agonists have been used in combination with other agents in the treatment of *prostatic* cancer (paragraph 003), which is an androgen sensitive cancer, and are *contraindicated*

for use in the treatment of estrogen-sensitive cancers, including breast and endometrial cancer (paragraph 008). Notwithstanding the Examiner's reliance on the teachings of Cameron, those teachings actually emphasize the patentability of the present invention and support Applicant's point- that compounds which have SERM activity (i.e., those used in the present invention) are favorably used in the present methods, whereas the prior art estrogen agonist compounds (such as those taught by van den Broek) are actually contraindicated for use in the present invention. Cameron teaches the person of ordinary skill to *avoid* estrogen agonists and to favorably use SERMS in breast cancer and uterine cancer, the precise support for patentability that Applicant relies on. However, Cameron suggests nothing with respect to any compound disclosed in van den Broek or any steroidal compound for that matter, and no such conclusion or inference could be drawn about the compounds used in the present invention. Cameron, contrary to the Examiner's view that it renders the present invention obvious, actually *supports* the patentability of the present invention.

Turning to the teachings of Palkowitz, this reference is relevant in that it, like Cameron, also teaches that the use of estrogen agonists in treating estrogen-sensitive (estrogen-dependent) cancers is contraindicated and to be avoided (column 2, lines 40-57). Palkowitz is otherwise related to naphthyl compounds which are completely unrelated structurally to the chemical structures of the compounds used in the present invention. Just as Cameron could be seen by one of ordinary skill in the art as supporting Applicant's claim for patentability, rather than the Examiner's position, so too does Palkowitz support the patentability of Applicant's invention. In short, Palkowitz does nothing to obviate the deficiencies of the teachings of van den Broek and Cameron in failing to suggest the present invention.

Regarding the teachings of Bodor, this reference teaches a number of compounds which are principally directed to certain salts of steroids having estrogenic activity which are used to enhance weight control activity. None of the compounds which are disclosed therein are related to the present invention and none of the compounds disclosed therein

or the disclosure provided, even allude to the compounds and methods of the present invention. Bodor, in the background of the invention section, does make an oblique reference to the use of estrogen compounds in the treatment of breast cancer, but otherwise does not provide any disclosure which is even relevant to the present invention. Taken to its logical conclusion, this reference at most suggests that the short-chain 11β compounds disclosed by van den Broek (not the present invention copounds) may be used to treat estrogen-sensitive cancers. Notwithstanding that teaching, which is not the present invention, it is noted that estrogen agonists actually are contraindicated for use in the treatment of estrogen-sensitive cancers (see the previously submitted declaration of Dr. Richard Hochberg), and although estrogen agonists historically were used in combination with other agents to treat cancer, that approach has been discontinued because of the tendency of that therapy to exacerbate or worsen the estrogen-sensitive cancer. Thus, the much earlier published Bodor must also be read in conjunction with the more contemporary Cameron and Palkowitz as supporting the relevance and benefit of the present invention. Bodor, in essence, does essentially nothing to cure the deficiencies of the other art in failing to suggest the present invention.

Note that with respect to the present invention, the compounds which are presently claimed in the methods of the present invention do not exhibit favorable activity as estrogen agonists of the prior art and are otherwise known as anti-estrogens. As discussed this activity is not discussed or suggested in van der Broek and is viewed negatively in any event. So, even if Bodor's 1986 disclosure is read in isolation (i.e., without reference to the later published Cameron and/or Palkowitz) in combination with van den Broek, and estrogen agonists are suggested for treating breast cancer (an approach which is actually counterproductive and deleterious to the breast cancer therapy outcome- see the previously submitted declaration of Richard Hochberg), the present compounds would not be used pursuant to those teachings because, as explained hereinabove, the present compounds *do not* exhibit estrogen agonist activity as called for by the Bodor treatment and as taught by van den Broek. Applying Bodor to the teachings of van den Broek would result in the use of the 11β short chain compounds in the

methods of Bodor and ***avoidance*** of the present method, because the compounds in the presently claimed methods would have been shown to exhibit *anti-estrogen activity* in the relevant assays, not the required (as taught by Bodor) estrogen agonist activity.

The position of the Examiner that it would have been obvious to use the presently claimed SERM compounds for the treatment of estrogen-dependent cancer because the prior art teachings suggest the use of the van den Broek estrogen agonist compounds for the treatment of estrogen-sensitive cancers as taught by Cameron, Palkowitz and Bodor is not cogent. As discussed above, the person of ordinary skill would not have recognized, from van den Broek, the SERM activity of the present invention, which is favorably used in the present invention. Whether one relies on the combined teachings of van den Broek and Bodor or the combined teachings of van den Broek and Bodor with either or both of Cameron and Palkowitz, one never provides the present invention, given that van den Broek and Bodor together rely on estrogen agonist activity which is not even present in the compounds used in the present invention. Reliance on van den Broek and Bodor, in combination with the teachings of Cameron and Palkowitz is misplaced and further confuses the teachings, given that the teachings of Cameron and Palkowitz completely contradict the teachings of Bodor and lead the person of skill away from using the estrogen agonists of van den Broek (again, not the estrogenic antagonists of the present invention) to treat breast cancer.

In sum, the person of ordinary skill would not have used the presently claimed compounds in methods requiring estrogenic agonist activity (Bodor) because the anti-estrogenic activity of the presently claimed compounds is actually *inconsistent* with the requirement for estrogenic agonist activity as taught by van den Broek and Bodor. If one adds the teachings of Cameron and Palkowitz one would not even use Broek and Bodor at all because such as an approach would be seen as ineffective and/or deleterious). If one were to rely on Cameron and Palkowitz, alone or in combination with Bodor, these references would not cure the deficiencies of van den Broek- they would actually point out the fallacy and inadequacy of using the van den Broek disclosed estrogen agonist

compounds to treat estrogen sensitive cancer as taught by Bodor. In either instance, if analyzed correctly, one of ordinary skill would not have recognized the SERM activity of the presently claimed compounds and not provided the present invention, because the unexpected SERM activity of the compounds used by the presently claimed methods was not even obliquely mentioned by van den Broek, or any of Cameron, Palkowitz and/or Bodor. It was not until the present application that the SERM activity of the presently claimed compounds became known and the benefit of such activity in the methods of the present invention which rely on such activity would have been realized.

As a separate note, there is no possible credible construction which can be made to suggest that the presently claimed invention is inherent to the disclosure of the prior art references, because, as explained, the person of ordinary skill would not have even used the presently claimed compounds because they were not suggested for use as SERMS and would not have the requisite activity (as estrogen agonists) as taught by van den Broek. Any reliance on the doctrine of inherency here is not cogent inasmuch as the doctrine of inherency requires the inevitability of the claimed method occurring as a consequence of practicing the invention which is disclosed and there is no disclosure in van den Broek or in any of Cameron, Palkowitz and/or Bodor which even arguably points to the use of the presently claimed compounds in the present methods. The use of the specifically disclosed estrogen agonist (short chain 11β) compounds of van den Broek, required by a cogent inherency analysis, and not used in the present invention (indeed, these compounds are specifically disclaimed) would clearly not result in the present invention. Applicant has not merely identified or even used inherent aspects of methods of treatment disclosed or otherwise suggested by *van den Broek* or the other references. In particular, discovering and using unidentified synthetic steroids possessing SERM activity for the purposes for which Applicant's claimed methods are administered was not suggested by, and in fact was contrary to, the teachings of the art.

Indeed, the present methods are not even accidentally practiced by relying on the teachings of the prior art given that van den Broek and Bodor teach the requirement for

estrogen agonist activity (i.e., the 11β short chain compounds which the presently claimed methods do not use and specifically exclude) and the remaining teachings of Cameron and Palkowitz teach that the use of estrogen agonists, as taught by Bodor and van den Broek should not even be used in the first place. *Cf. Rapoport v. Dement, et al.*, 254 F.3d 1053, 1059, 59 U.S.P.Q. 2d 1215 (Fed. Cir. 2001). Given the absence of teaching of SERM activity in van den Broek, Applicant respectfully submits that the present invention could not possibly have been made from the teachings of the prior art.

It is respectfully submitted that the presently claimed invention is patentable. The unexpected activity of the claimed compounds as SERMS is neither disclosed nor suggested by the art of record and this unexpected activity has been put to use in claimed methods which clearly rely on and distinguish over the art based upon this unexpected activity.

Given what was known in the prior art and their own knowledge, those of ordinary skill in the art at the time of the present invention would have reasonably believed that the presently claimed methods would have failed to achieve the purposes of the prior art taught methods *and* the purpose for which the currently claimed methods are applied. *See Takeda Chem. Indust. v. Alpharma Pty Ltd.*, 492 F.3d 1350; 2007 U.S. App. LEXIS 15349; 83 U.S.P.Q.2D (BNA) 1169 (Fed. Cir. 2007), *cert. denied*, 2008 U.S. LEXIS 3015 (U.S., Mar. 31, 2008). The present invention is clearly patentable over the disclosed prior art.

For the above reasons, Applicants respectfully assert that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

No fee is due for the presentation of the amendments made herein. A petition for an extension of time is enclosed as is authorization to debit Deposit Account 04-0838 for

the requisite fee. Please charge any additional fee due or credit any overpayment to Deposit Account No. 04-0838.

If the Examiner believes that discussing the present application with the undersigned attorney may materially advance the prosecution of this application, She is cordially requested to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

Coleman Sudol Sapone, P.C.

Enc.

December 6, 2011

By: _____
Henry D. Coleman
Regis. No. 32,559
714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
(203) 366-3560

CERTIFICATE OF FACSI MILE TRANSMISSION

I hereby certify that this correspondence is being sent by facsimile transmission to Examiner Barbara Badio in Group Art Unit 1628 of the United States Patent and Trademark Office, at P.O. Box 1450 Alexandria, Virginia 22313-1450" on December 9, 2011.

_____
Henry D. Coleman

United States Court of Appeals for the Federal Circuit

UNIGENE LABORATORIES, INC. AND UPSHER-SMITH LABORATORIES, INC.,
Plaintiffs-Appellees,

v.

APOTEX, INC. AND APOTEX CORP.,
Defendants-Appellants.

2010-1006

Appeal from the United States District Court for the Southern District of New York in case no. 06-CV-5571, Judge Robert P. Patterson, Jr.

Decided: August 25, 2011

BRUCE C. HAAS, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for plaintiffs-appellees. With him on the brief was STEVEN C. KLINE.

MANNY D. POKOTILOW, Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd., of Philadelphia, Pennsylvania, argued for defendants-appellants. With him on the brief were ROBERT S. SILVER, JAMES J. KOZUCH and MARC B. BASSLER. Of counsel was WILLIAM JOSEPH CASTILLO.

Before RADER, *Chief Judge*, MOORE, and O'MALLEY
Circuit Judges.

RADER, *Chief Judge.*

The United States District Court for the Southern District of New York heard a dispute between Apotex, Inc. and Apotex Corp. ("Apotex"), the appellants, and Unigene Laboratories, Inc. and Upsher-Smith Laboratories, Inc. (collectively, "Unigene"), the appellees, over claim 19 of U.S. Patent No. RE40,812E ("'812E patent"). On cross-motions for summary judgment, the district court granted Unigene's motion that the patent would not have been obvious at the time of invention. *Unigene Labs., Inc.,v. Apotex, Inc.* ("Summary Judgment Opinion"), No. 06-CV-5571, Dkt. No. 175, slip op. at 28-29 (S.D.N.Y. Aug. 31, 2009). The trial court also denied Apotex's motion to breach the attorney-client privilege under the crime-fraud exception. *Unigene Labs., Inc.,v. Apotex, Inc.* ("Crime-Fraud Opinion"), No. 06-CV-5571, Dkt. No. 89, slip op. at 18 (S.D.N.Y. Feb. 4, 2008). In addition, the district court determined that Apotex had waived several counterclaims. *Unigene Labs., Inc.,v. Apotex, Inc.* ("Counterclaim Opinion"), No. 06-CV-5571, 2010 WL 2730471 (S.D.N.Y. July 7, 2010). Because the district court correctly decided all of these motions, this court affirms.

I.

Unigene owns the '812E patent through assignment from inventor Dr. William Stern ("Stern"). The '812E patent is a reissue of U.S. Patent No. 6,440,392 ("'392 patent"). The reissue occurred on June 30, 2009, while this case was before the district court.

Covered by the '812E patent, Fortical® is an Food and Drug Administration ("FDA") approved pharmaceutical nasal spray with the active ingredient salmon calcitonin

("salmon calcitonin" or "calcitonin"). Unigene filed for FDA approval under 21 U.S.C. § 355(b)(2) and now holds the New Drug Application ("NDA") for Fortical®. Unigene's NDA claims Miacalcin® as its reference drug, meaning that for FDA approval, Unigene had to prove that Fortical® was a bioequivalent of Miacalcin®. Upsher-Smith is the exclusive patent licensee, with rights to market and sell Fortical® in the United States. Fortical® treats, among other things, postmenopausal osteoporosis.

Fortical® is a bioequivalent of Novartis International AG's Miacalcin® calcitonin nasal spray. Miacalcin® has been marketed since 1995, before the '812E patent's February 4, 2000 priority date. Unigene developed Fortical® as an alternative to Miacalcin®.

Both Miacalcin® and Fortical® use salmon calcitonin at a concentration of 2,200 I.U./mL as their active ingredient. Salmon calcitonin is a natural polypeptide hormone. Calcitonins help regulate calcium ions in the blood and therefore address calcium-related conditions like osteoporosis. To be effective, polypeptides, like salmon calcitonin, must reach the bloodstream. Delivery to the bloodstream, however, is not easy because calcitonins are readily degraded by bodily fluids, are relatively unstable in pharmaceutical compositions, and are poorly absorbed through tissues. Miacalcin® and Fortical® are both nasal sprays.

Fortical® and Miacalcin® have different formulations. For instance, Miacalcin® also contains 8.5 mg of sodium chloride, which acts as a tonicity agent; nitrogen, which acts as a sparging agent; hydrochloric acid, which acts as a pH adjuster; and purified water, which acts as a carrier. Of particular importance to this appeal, Miacalcin® contains 0.10 mg of benzalkonium chloride ("BZK") which functions as a preservative, absorption enhancer, and

surfactant. In contrast, Fortical® contains 20 mM of citric acid, which functions as an absorption enhancer and stabilizer/buffer; polyoxyethylene(2) sorbitan monooleate ("polysorbate 80"), which acts as a surfactant; and phenylethyl alcohol and benzyl alcohol, which serve as preservatives.

Apotex, a Canadian pharmaceutical company, filed Abbreviated New Drug Application ("ANDA") No. 078200 with the FDA on June 1, 2006. Apotex's ANDA certified under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("paragraph IV certification") intends to make, use, offer to sell, sell, and/or import a generic version of Unigene's Fortical® product before the expiration of the '812E patent. Because a paragraph IV certification is an act of infringement under 35 U.S.C. § 271(e)(2), *see also Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004), Unigene lodged a Complaint for infringement in the district court. The only asserted claim in the litigation is claim 19. Claim 19 reads:

> A liquid pharmaceutical composition for nasal administration comprising about 2,200 MRC units of salmon calcitonin, about 20 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% polyoxyethylene(2) sorbitan monooleate

'812E patent col.18 ll.1-5.

Apotex's original Answer of September 20, 2006 contained numerous affirmative defenses. In addition to allegations of invalidity under 35 U.S.C. §§ 101, 102, 103, and 112, Apotex alleged noninfringement and inequitable conduct. The inequitable conduct assertions cited the failure to disclose an allegedly material piece of prior art and making allegedly misleading statements during

patent prosecution. Apotex filed an Amended Answer on May 8, 2007 with two more inequitable conduct allegations, one based on an error in Table 3 of the '392 patent and another based on the failure to disclose a piece of prior art.

In September 2007, during fact discovery, Apotex moved to breach Unigene's attorney-client privilege under the crime-fraud exception. In support of these allegations, Apotex referred to Unigene's alleged failure to disclose U.S. Patent No. 5,912,014 ("'014 patent") to the U.S. Patent and Trademark Office ("Patent Office") and to errors in Table 3 of the '392 patent, the same conduct upon which Apotex premised some of its inequitable conduct claims at issue in this appeal.

The prior art '014 patent, with Dr. Stern as a co-inventor, carries the title "Oral Salmon Calcitonin Pharmaceutical Products." The '014 patent claims enteric-coated solid pharmaceutical formulations of salmon calcitonin, administered orally. The '014 patent discloses a solid oral tablet that the specification touts as a more convenient and comfortable dosage method for patients. The '014 patent teaches an oral formulation that resists degradation during the digestion process to keep the salmon calcitonin active. The '014 patent discloses experiments measuring the effects of citric acid on buffer pH, bioavailability of salmon calcitonin, and absorption of salmon calcitonin in the presence of enhancers. These experiments injected 0.5 mL of liquid formulation containing citric acid, taurodeoxycholic acid, mannitol, and calcitonin into the exposed duodenum of anesthetized rats. The experiments showed an increase in calcitonin's bioavailability when the amount of citric acid was increased and noted that bioavailabilty was "minor" in the presence of enhancers when compared to citric acid alone.

Table 3 of the '392 patent, reproduced below, shows the effect of citric acid concentration on the stability of salmon calcitonin stored at 50°C. Table 3 shows the percentage of calcitonin in formulations with different amounts of citric acid over fifteen days. As published '392 patent, Table 3 had two errors, indicated by the strike-through lines:

EFFECT OF THE CONCENTRATION OF CITRIC ACID ON THE STABILITY OF sCT STORED FOR VARYING PERIODS AT 50° C (Percent sCT Recovered)					
Citric Acid (pH 3.7)	0 mM	10 mM	~~20~~ 25 mM	50 mM	100 mM
Days at 50° C					
0	100	100	100	100	100
3	83	94	91	90	87
6	53	90	87	83	77
9	24	82	78	73	66
15	22	74	68	61	~~20~~ 52

J.A. at 31. The error on the top axis, characterized as clearly typographical in nature by the district court, labels a column "20 mM" instead of "25 mM." Second, the point of Apotex's allegations, a data point on the table reads 20 percent instead of the 52 percent actually measured. The column containing the second error shows that a salmon calcitonin solution with 100 mM of citric acid degrades over time, as the percentages of recovered calcitonin decrease from 100 percent to 52 percent over time. Whether the 15 day measurement is 20 percent or 52 percent, the recovery is still below the 66 percent recovered after 9 days.

The record indicates that Dr. Stern immediately informed the Patent Office when he became aware of the errors in Table 3. Specifically, Dr. Stern submitted a declaration on September 7, 2007, explaining an "inadvertent error during automated data analysis." He explained

further that the error did not affect the trend of salmon calcitonin reduction.

The district court declined to find that these errors or non-disclosures were sufficient to pierce the attorney-client privilege. The district court found the '014 patent to be either immaterial to the '392 patent or cumulative to the other cited references. *Crime-Fraud Opinion*, at 11. While both the '014 patent and '392 patent related to pharmaceutical formulations of salmon calcitonin, the district court found that the '392 patent's formulations were "considerably different" than formulations in the '014 patent and were, therefore, immaterial. *Crime-Fraud Opinion*, at 11. The district court also found that Apotex's proffered evidence of fraudulent intent regarding the '014 patent was insufficient to establish a prima facie case of fraud. *Id.* at 12.

The district court also found that the errors in Table 3 of the '392 patent were immaterial. *Id.* at 14-15. The district court found the corrected version of the table consistent with Unigene's assertions at the Patent Office. *Id.* at 16. The district court concluded that the errors were not material with respect to patentability or common law fraud. *Id.* The district court also determined that evidence of Stern's submission of a second declaration to clarify errors in Table 3 lacked deceptive intent, making that conduct insufficient to support an assertion of common law fraud. *Id.* at 17-18.

Unigene and Apotex cross-moved for summary judgment on obviousness. The Patent Office granted reissue of the '392 patent on June 30, 2009, at which point the district court granted Unigene's motion to amend the Complaint to replace all references to the '392 patent with the reissued '812E patent. Apotex filed an Answer to Unigene's Amended Complaint on July 20, 2009 that

included several additional counts of inequitable conduct. Without addressing these new claims, the district court granted Unigene summary judgment of nonobviousness and entered judgment.

The district court found that the '812E patent would not have been obvious at the time of invention as a matter of law. *Summary Judgment Opinion* at 29. In considering forty-plus pieces of prior art submitted by Apotex (also considered by the Patent Office during prosecution of the '812E patent), the district court found that no prior art teaches using 20 mM citric acid to achieve "both shelf stability and enhanced bioavailability" in a nasal salmon calcitonin formulation. *Summary Judgment Opinion* at 15.

The district court also found that it would not have been obvious to a person of ordinary skill in the art to modify Miacalcin® to reach the formulation of claim 19. The record shows that a person of ordinary skill was an individual with a masters degree in chemistry, pharmaceutical chemistry, biochemistry, or a similar field with at least eight years of practical experience in pharmaceutical liquid dosage form development, or an individual with a Ph.D. in the same fields with at least four years of practical experience in pharmaceutical liquid dosage form development. Specifically, the district court determined first that BZK serves as an absorption enhancer, a preservative, and a surfactant in Miacalcin®. Then, the court relied on expert testimony to conclude that a person of ordinary skill would have been motivated to find other FDA-approved compounds that serve as both absorption enhancers and preservatives of calcitonin. Further, the district court found that the prior art taught alternative methods of improving bioavailability and absorption of calcitonin.

In response to the court's summary judgment rulings, Apotex moved for reconsideration in light of its counterclaims of inequitable conduct. The district court granted Apotex's motion to consider its counterclaims. Nonetheless the district court re-entered judgment for Unigene. The district court held that all of Apotex's defenses and counterclaims, those asserted in 2006-07 and those Apotex sought to add in 2009, had been conceded, waived, barred, abandoned, or improperly raised. Apotex appeals the district court's rejection of the three added inequitable conduct counterclaims ("Count XII, Count XIII, and Count XIV"). This court has jurisdiction under 35 U.S.C. § 1295(a)(1).

II.

This court applies its own law to review a district court's application of the crime-fraud exception to the attorney-client privilege. *In re Spalding Sports Worldwide, Inc.*, 203 F.3d 800 (Fed. Cir. 2000). This court reviews a district court's determination of material protected by the attorney-client privilege for an abuse of discretion. *Apotex Corp. v. Merck & Co.*, 507 F.3d 1357, 1362 (Fed. Cir. 2007).

A party must establish *Walker-Process* fraud, also known as common law fraud, to successfully pierce the attorney-client privilege under the crime-fraud exception. *See Walker-Process Equip., Inc. v. Food Mach. & Chem. Corp.*, 382 U.S. 172, 177 (1965). A finding of common law fraud in the patent context "must be based on independent and clear evidence of deceptive intent together with a clear showing of reliance." *Spalding*, 203 F.3d at 803; *see Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059, 1070 (Fed. Cir. 1998) (holding that both fraudulent misrepresentations and omissions can support a finding of common law fraud). Such independent and clear evidence

must establish a prima facie case of fraud, which is "generally held *not* to exist" unless the accusing party can show:

> (1) a representation of material fact, (2) the falsity of that representation, (3) the intent to deceive or, at least, a state of mind so reckless as to the consequences that it is held to the equivalent of intent (scienter), (4) a justifiable reliance upon the misrepresentation by the party deceived which induces him to act thereon, and (5) injury to the party deceived as a result of his reliance on the misrepresentation

Spalding Sports, 203 F.3d at 807 (citing *Nobelpharma*, 141 F.3d at 1069-70). This court need only examine Apotex's proffered evidence of intent to uphold the district court's refusal to invoke the crime-fraud exception.

The record does not show clear evidence of intent for either of the alleged fraudulent acts by Unigene. As noted by the district court, the record contains only an essentially "unsupported allegation" that Dr. Stern intentionally left the '014 patent off of the initial information disclosure statement of the '392 patent. *Crime-Fraud Opinion*, at 12. The second allegation of fraud rests on a similarly flimsy foundation.

In the first place, the typographical error in Table 3 of the '392 patent, corrected on reissue, does not call for the extreme remedy of piercing the attorney-client privilege. The district court found the "evidence tend[ed] to prove that this error was an honest mistake, though perhaps a careless one." *Id.* at 16. Indeed, Dr. Stern submitted a declaration during the reissue proceedings to explain the error in Table 3. Further, as the trial court found, the

error itself did not alter the arguments made by Unigene to the PTO. Accordingly, the district court concluded that the record did not show any evidence of intent to deceive the Patent Office. *Id.* at 18.

The district court did not abuse its discretion in these findings on the crime-fraud exception to the attorney-client privilege. This court need not reach the district court's materiality determinations because the record is devoid of sufficient intent evidence.

III.

This court reviews a district court's denial of a party's motion to amend its pleadings under the law of the regional circuit. *Panduit Corp. v. All States Plastic Mfg. Co.*, 744 F.2d 1564, 1575 (Fed. Cir. 1984). The United States Court of Appeals for the Second Circuit reviews a district court's denial of a request to amend pleadings for an abuse of discretion. *Parker v. Columbia Pictures Indus.*, 204 F.3d 326, 339-40 (2d Cir. 2000). Apotex appeals the court's refusal to add Counts XII, XIII, and XIV to its Answer to Unigene's Amended Complaint. Apotex does not challenge the district court's rulings with respect to the allegations of inequitable conduct asserted in its Original and First Amended Answers. The district court's decision was based on its determination that Unigene's Amended Complaint did not change the scope of the original Complaint and therefore did not provide an opportunity for Apotex to expand the breadth of its affirmative defenses or counterclaims.

The record shows that the district court acted well within its discretion in finding that Apotex's added counterclaims were not "colorable grounds for relief." *Blaskiewicz v. Cnty. of Suffolk*, 29 F. Supp. 2d 134, 138 (E.D.N.Y. 1998) (citation omitted). The trial court is especially well positioned to assess whether the Amended

Complaint it authorized materially changed the scope of the original Complaint. Counts XII, XIII, and XIV all relate to inequitable conduct. The district court found that the filing of an Amended Complaint, which merely renamed the patent in suit post-reexamination, did not so materially alter the proceedings as to authorize previously unasserted counterclaims. The district court found Count XII improper because, *inter alia*, the new claim provided inadequate notice to Unigene. The district court barred Counts XIII and XIV, which mirror Apotex's crime-fraud allegations, based on the same fatal absence of materiality and intent already addressed in the Crime-Fraud Opinion. This court agrees that the record shows insufficient evidence of fraudulent intent and erects an insurmountable obstacle to Apotex's new counterclaims. Accordingly, the district court did not abuse its discretion by denying Claims XII, XIII, and XIV.

IV.

This court reviews the district court's grant of summary judgment without deference. *Eisai Co. Ltd. v. Dr. Reddy's Labs.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008). Summary judgment is appropriate if the movant can show both the absence of genuine issues of material fact and entitlement to judgment as a matter of law. Fed. R. Civ. P. 56(c). This court reviews the evidence in the light most favorable to the party opposing the motion, with all doubts resolved in favor of the nonmovant. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1360-61 (Fed. Cir. 2008).

Obviousness under 35 U.S.C. § 103(a) is a legal question based on underlying factual determinations. *Eisai*, 533 F.3d at 1356 (citing *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1478, 1479 (Fed. Cir. 1997)). An obviousness analysis measures the difference between the

claimed invention and the prior art to determine whether "the subject matter as a whole would have been obvious at the time the invention was made" to a person having ordinary skill in the art. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006) (citing *In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006)). The factual underpinnings, often referred to as the *Graham* factors, include 1) the scope and content of the prior art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) evidence of secondary factors, also known as objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention. *Id.* at 421 (describing that a person of ordinary skill possesses "ordinary creativity, [and is] not an automaton"); *see also Bayer Schering Pharm. AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009) (Newman, J., dissenting) ("The statutory criterion is whether the invention would have been obvious to persons of ordinary skill at the time of the invention, not whether it is sufficiently simple to appear obvious to judges after the discovery is finally made . . . .").

A person of ordinary skill at the time of the invention interprets the prior art using common sense and appropriate perspective. *KSR*, 550 U.S. at 421. In *KSR* the Supreme Court observed:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Id. Accordingly, when design need and market pressure may dictate a commonsensical path using a finite number of identified predictable solutions to one of ordinary skill, deviations from that path are likely products of innovation.

This court has observed that teachings from prior art, suggestions beyond the literal teachings of those art references, or even motivations from the store of common knowledge of one of ordinary skill in the art field ("TSM")—flexibly viewed and applied—provide the sources of evidence that an ordinary skilled artisan might have found and combined at the time of the invention. *Ortho-McNeil*, 520 F.3d at 1364-65 ("[A] flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis . . . ."); *see also KSR*, 550 U.S. at 419 ("The obviousness analysis cannot be confined by a formalistic conception of the words, teachings, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.").

In this case, the patent claims a new composition or formulation to deliver an FDA-approved active ingredient. Thus, the claimed invention is not obvious if a person of ordinary skill would not select and combine the prior art references to reach the claimed composition or formula-

tion. *Eli Lilly v. Zenith Goldline Pharm.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("to establish a prima facie case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention").

To render a claim obvious, prior art cannot be "vague" and must collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution. *Bayer Schering.*, 575 F.3d at 1347. Indeed, "most inventions that are obvious were also obvious to try," *id.*, and a combination is only obvious to try if a person of ordinary skill has "a good reason to pursue the known options." *KSR*, 550 U.S. at 421. When a field is "unreduced by direction of the prior art," and when prior art gives "no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful," an invention is not obvious to try. *Bayer Schering*, 575 F.3d at 1347 (citing *O'Farrell*, 853 F.2d at 903); *see also Ortho-McNeil*, 520 F.3d at 1364 (stating the number of options must be "small or easily traversed").

A prima facie case of obviousness in the chemical arts is often based on a known compound, called a "lead compound," which serves as a starting point for a person of ordinary skill developing the claimed invention. *See Eisai*, 533 F.3d at 1357. Where the patent at issue claims a chemical compound, a lead compound is often used to show structural similarities between the claimed compound and prior art. *Id.* (citing *Eli Lilly*, 471 F.3d at 1377). In the context of a composition or formulation patent where the patented formulation was made to mimic a previously FDA-approved formulation, the functional and pharmaceutical properties of the "lead compound" can be more relevant than the actual chemical structure (though not always mutually exclusive). Thus,

the term "reference composition" is more appropriate than "lead compound" when considering obviousness for a chemical composition that the infringer deliberately imitates. In this case, Miacalcin® serves as the "reference composition" for Dr. Stern's development of the claimed composition. In Miacalcin®, BZK acts as a preservative, absorption enhancer, and surfactant. Claim 19 of the '812E patent is the result of Dr. Stern's effort to design around Miacalcin®. It is undisputed that "about 20 mM citric acid" in claim 19 functions as an absorption enhancer and surfactant in Fortical®.

Although claim 19 does not assign any particular functionality or property to its list of components, a person of ordinary skill, someone in the field of pharmaceutical liquid dosage form development, would have had reasons—specifically, design need and market demand—to create an FDA-approved liquid nasal composition that delivers salmon calcitonin. *See KSR*, 550 U.S. at 421. In this case, the design need is to achieve a bioequivalent composition. The market demand is to achieve a composition that treats the same symptoms as the reference formulation. Specifically, on February 4, 2000, someone developing a pharmaceutical nasal liquid dosage form with the active ingredient of salmon calcitonin would have known that a bioequivalent of Miacalcin®, largely determined by equivalent bioavailability of salmon calcitonin, would have the best chance to gain FDA approval quickly. *See* 21 § C.F.R. 320.23(b) ("Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions . . . ."); *id.* ("Bioavailability means the rate and extent to which the active ingredient or active moiety

is absorbed from a drug product and becomes available at the site of action."). Creating a bioequivalent of Miacalin® would allow approval of the new pharmaceutical liquid dosage form as an ANDA under 21 U.S.C. § 355(j)(2)(A)(vii) or an NDA under 21 U.S.C. § 505(b)(2)—both enjoying the additional advantage of using the clinical data or literature submitted in support of Miacalcin®. Alternatively, a composition requiring full clinical trials to demonstrate safety and effectiveness would require approval as an NDA under 35 U.S.C. § 505(b)(1), a significantly longer process. This court appreciates that the Hatch-Waxman Act encourages and rewards replication of protected compounds in some circumstances—an activity that rarely, but can, lead to innovative products.

While claim 19 contains several excipients in addition to salmon calcitonin, at oral argument, Unigene acknowledged that "citric acid is a very important part" of claim 19's case for inventiveness and nonobviousness. Oral Argument at 21:48-22:00, available at *http://www.cafc.uscourts.gov/oral-argument-recordings/2010-1006/all.* While the district court found other elements in combination were also nonobvious, this court agrees that the inclusion of "about 20 mM citric acid" in the composition provides the strongest case for nonobviousness.

Apotex asserted for the first time at oral argument that claim 19 is obvious in light of three pieces of prior art: Miacalcin®, the Day reference, and the '014 patent. *Id.* at 4:50. As discussed above, Miacalcin® serves as the reference composition.

On the basis of the record before this court, this court agrees that no reasonable juror could conclude that the '014 patent would give a person of ordinary skill sufficient reason or motivation to use about 20 mM citric acid in a

liquid nasal salmon calcitonin composition. *See KSR*, 550 U.S. at 421. The '014 patent claims a solid oral dosage of salmon calcitonin, not a liquid formulation. While the experiments discussed in the '014 patent found that "the bioavailability of salmon calcitonin increased nearly 10 fold when the amount of citric acid in the formulation was increased only 5 fold," '014 patent col.11 ll.33-35, a person of ordinary skill (not Dr. Stern, a co-inventor of the '014 patent) would not glean from the '014 results a reason to use about 20 mM citric acid in a nasal calcitonin formulation. The '014 patent itself describes a solid oral formulation of salmon calcitonin. Although the '014 patent mentions citric acid, that discussion refers to concentrations of citric acid much higher than those in claim 19. Moreover, the '014 patent examined citric acid for bioavailability in the context of a liquid injection into a rat duodenum, not a human use in a liquid pharmaceutical formulation. These significant differences would not cause a person of ordinary skill to replace BZK in Miacalcin® with 20 mM of citric acid in the normal course of research and development.

To a person of ordinary skill in the art, citric acid, even at about 20 mM concentrations, would not be an obvious substitute for BZK's functions as an absorption enhancer and as a surfactant because citric acid has a vague role in even the closest prior art. *See Eli Lilly*, 471 F.3d at 1380. U.S. Patent No. 5,124,315 ("'315 patent") describes liquid pharmaceutical compositions for nasal administration containing a polypeptide as an active ingredient. Example 5 of the '315 patent uses 20.5 mM of citric acid in a liquid nasal formulation containing salmon calcitonin as its active ingredient. '315 patent col.3 l.43. The '315 patent makes clear however that "citric acid was not used as an absorption enhancing agent, but it is

merely the acidic component of the buffer." *Id.* at col.4 ll.18-23.

In fact, the '315 patent teaches away from using about 20 mM citric acid as an absorption enhancing agent or stabilizing agent in a liquid formulation with a salmon calcitonin active ingredient. The '315 patent discusses U.S. Patent No. 4,476,116 ("'116 patent"), directed toward nasal compositions having enhanced peptide absorption. The '116 patent lists over fifty examples, including citric acid, of pharmaceutically acceptable chelating agents to serve as absorption agents. '116 patent col.11 l.1. Both parties agree that the '315 patent reports that the compounds listed in the '116 patent yielded "discouraging" test results, and that "only ammonium tartrate is a satisfactory stabilizing agent for liquid nasal compositions containing polypeptides as active ingredient [sic]." '315 patent col.2 ll.13-16, 19-21. One of ordinary skill in the art reading the '315 and '116 patents would have considered about 20 mM citric acid undesirable in a liquid nasal formulation containing salmon calcitonin.

The Day reference, a publication about pharmaceutical preformulation and formulation, lists benzyl alcohol and phenylethyl alcohol as two of nine listed preservatives on a table of "Excipients used in aqueous nasal products." J.A. at 11397. BZK is one of the nine listed preservatives in Day, along with benzethonium chloride, chlorobutanol, methylparaben, phenylmercuric acetate, propylparaben, and thimerosal. Citric acid is not included in the list of preservatives, but appears instead as a pH adjuster or buffer. The Day reference also lists polysorbate 20 and 80 as one of three surfactants used as excipients in aqueous nasal products. With reference to this prior art, there is no evidence to support the conclusion that a person of ordinary skill would expect a combination of citric acid, benzyl alcohol, phenylethyl alcohol, and

polysorbate 80 to contain a buffer, pH adjuster, preservative, and surfactant, but no absorption enhancer or excipient to promote bioavailability.

Thus, the "about 20.0 mM citric acid" limitation alone supports the district court's grant of summary judgment of nonobviousness. When used as an absorption enhancer in the '116 patent, citric acid was one of over fifty options. *See KSR*, 550 U.S. at 421. Further, when the prior art used citric acid at about 20 mM, as in the '315 patent, it was used only as a buffer. There is no genuine dispute of material fact that a person of ordinary skill attempting to make a liquid composition to deliver salmon calcitonin into a human body through nasal administration, would not have considered using about 20 mM citric acid with the narrowly claimed amounts of benzyl alcohol, phenylethyl alcohol, and polysorbate 80, because the formulation would not be expected to perform properly to meet the specificity of a pharmaceutical use. Thus, even accepting that there was a design need and market pressure to develop a pharmaceutical formulation that is bioequivalent to Miacalcin®, there is no evidence in the record that claim 19 would be an obvious solution to those motivations.

V.

Accordingly, this court affirms the district court's grant of summary judgment of nonobviousness in favor of Unigene, affirms the district court's denial of summary judgment of obviousness, affirms the district court's denial of Apotex's crime-fraud motion, and affirms the district court's dismissal of Apotex's new claims and defenses.

AFFIRMED

Each party shall bear its own costs.